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Childhood Hodgkin's Disease in Campinas, Brazil

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Purpose: Little clinical information about Hodgkin's disease in children is available from poor countries. The object of this study is to evaluate our data in Campinas, Brazil and hope "to make one dot on the geographic map of this disease more clear." *Patients and Methods:* Between 1978 and 1988, 46 patients under the age of 17 years with biopsy-proven Hodgkin's Disease (HD) were referred for evaluation at Centro Boldrini in Campinas, São Paulo state, in Brazil. Thirty-seven of them were treated and followed-up only at this Center and are the subjects of this analysis. All the original histological slides were obtained, reviewed, and classified according to the Rye system. Staging procedures included exploratory laparotomy in 33 of 37 children, but none had lymphangiography. Treatment was individualized until January 1986 when the German protocol was adopted. *Results:* Nineteen cases were classified as nodular sclerosis, 14 as mixed cellularity, and three as lymphocyte depleted. Mean age was 7 years; male/female ratio was 2:1. Fifty percent were advanced stages III and IV and 46% (17/37) had at least one of the systemic B symptoms. Mean follow-up was 81 months (range from 41 to 174 months). Five-year actuarial overall survival was 78%. Two children (5%) had acute myeloid leukemia at 25 and 49 months after diagnosis. *Conclusions:* Although distribution of histological subtypes of our cases is similar to other reports in developed countries, as well as percentage of advanced stages III/IV, our patients fared worse when compared to those reports. The reason for this continues to remain unclear but it does not seem to be related to histology subtypes.

Key words: Hodgkin's disease, lymphoma in children, histological subtypes

INTRODUCTION

There has been a vast amount of information published in the medical literature regarding Hodgkin's disease (HD). Almost all clinical information comes from developed countries and concern adult patients. Childhood HD (CHD) is less frequent and consequently there has been less information regarding natural history, pathology, response to therapy, and complications.

Over the past two decades, dramatic improvements in overall survival and relapse-free survival in the range of 80 to 90% at 5 years have been reported for adult and CHD. Treatment of CHD has not only improved survival but also decreased late complications, such as disturbed growth of irradiated bones and soft tissues, second cancer, and gonadal dysfunctions, thanks to less aggressive alternative protocols.

Geographically it has been mentioned for the last 20 years that there is a different epidemiologic pattern of HD in underdeveloped countries when compared to developed ones. In developed countries, the majority of patients, adults and children, have presented with asymptomatic, low-stage disease and nodular sclerosis (NS) histologic subtype. Conversely, it has been said that in Third World countries there is a substantially higher incidence of symptomatic, advanced stage disease and predominance of mixed cellularity (MC) and lymphocyte depleted (LD) subtypes, associated with poor prognosis [1,2]. Third World pattern of HD has been also reported in Los Angeles, CA, among people of lower socio-economic status [3].

The fact is that little clinical information about HD is available from poor countries and that is particularly true for CHD [2,4–8]. The purpose of this study is to report on 37 cases of CHD treated in Campinas-SP, Brazil. Clinico-pathological information is given, as well as results of therapy and median follow-up of 81 months.

PATIENTS AND METHODS

Centro Dr. Domingos Boldrini is a philanthropic institution that attends to patients from all socio-economic

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levels in Campinas-SP, Brazil. All cases of CHD proven by biopsy and referred to the Center, seen between September 1978 and October 1988, were included. In order to enter this analysis, patients should have been staged, treated, and followed-up only at the Center.

In this retrospective and non-randomized study, clinical records were reviewed and the following data recorded: age, sex, staging of disease, histopathological subtypes at diagnosis, presence of B symptoms, type of therapy, response to therapy, relapse, current disease status, last date of follow-up, and cause of death when applicable. Actuarial survival and disease free survival (DFS) curves were calculated by the Kaplan-Meier product limit method [9]. Death without disease was considered as an event in calculating survival and censored in calculating DFS. DFS curves considered only patients that achieved complete remission. Study was closed for analysis in November 1993.

Clinical and pathological staging were accomplished according to the Ann Arbor system [10]. Staging procedures included clinical history, physical examination, chest x-ray, liver-spleen scans, computed tomography and/or ultrasound of abdomen and pelvis. Lymphangiography was not utilized in any case. Surgical staging was generally indicated with bone marrow biopsy and exploratory laparotomy and splenectomy. Since January 1986, the Center adopted the German protocol for CHD [11], according to which lymphangiography is not routinely indicated. Exploratory laparotomy is indicated only when computer tomography or ultrasound of the abdomen or pelvis is suspected to be positive, and/or mediastine is considered positive for HD.

Before utilization of the German protocol, children were treated according to the medical literature with: 1) extended field radiotherapy (RT) alone (total doses between 36 gray (Gy) and 40 Gy) in a cobalt unit; 2) combination of chemotherapy (CT) with nitrogen mustard, Vincristine, procarbazine, prednisone (MOPP) or MOPP/doxorubicin, bleomycin, vinblastine, DTIC (ABVD) and RT. After 1986, the German protocol was utilized as follows: 1) stages I, IIA—two cycles of CT (2 × Vincristine, procarbazine, prednisone, doxorubicin (OPPA) + involved field radiotherapy, dose of 35 Gy; 2) stages IIB, IIIA—four cycles of CT (2× (OPPA + 2× cyclophosphamide, Vincristine, methotrexate, prednisone (COMP)) + involved field radiotherapy, 30 Gy; 3) stages IIIB, IV—six cycles of CT (2× OPPA + 4× COMP) + involved field radiotherapy, 25 Gy. In all groups a boost of 5 to 10 Gy of radiation was permitted in cases of clinical residual tumor after chemotherapy.

All histological blocks (17 cases from the University of Campinas and 20 from elsewhere) were obtained for review, on routinely stained sections (H&E), by two independent specialized hematopathologists that do not work in the Center. Meticulous subclassification was performed using the criteria of Lukes and Butler [12,13] since an appropriate pathology review was one main point of this study.

TABLE I. Ann Arbor Stages of the 37 Patients at Diagnosis

	Systemic symptoms		
	A	B	Total
Stage			
I	5	3	8
II	7	4	11
III	8	8	16
IV	0	2	2
Total	20	17	37

RESULTS

Between 1978 and 1988, 46 children with HD were treated at Centro Boldrini but 37 entered this study because nine had been partially managed elsewhere. The male/female ratio was 25/12 or 2:1. Mean age was 7 years (range between 18 months and 17 years). Twenty of the 37 (54%) were aged between 5 and 9 years.

Table I summarizes the staging at presentation: 19 were stages I or II and 18 were stages III or IV. Almost half (46% or 17/37) of the patients presented with one or all three systemic B symptoms of fever, night sweats, or weight loss. Except for four children, the other 33 had exploratory laparotomy for staging. The four exceptions included three children with no such indication according to the German protocol, and one child, stage IIIB, with extensive infra-diaphragmatic disease where the surgery was considered useless.

Two children were treated with RT alone (extended field, 36Gy to 40 Gy); eight with a combination of MOPP and RT (15Gy to 35Gy); 10 with a combination of MOPP/ABVD and RT; and 17 were treated according to the German protocol.

Time of follow-up ranged from 41 months to 174 months, mean time of 81 months. All of the 37 patients had complete follow-up. Actuarial curves of overall survival and DFS are shown in Figure 1. Overall survival at 5 years was 78% for the entire population and DFS was 79% for the 33 children that achieved complete remission. Eight patients (22%) had some failure of treatment: four (11%) never achieved complete remission and died of progressive disease after 12, 15, 25, and 35 months of diagnosis. They were initially staged as IIIB, IIB, IIIB, and IVB, respectively, and the histological subtypes were 3 NS and 1 LD. One of them was a 9 year old, NS type, stage IIB, treated with 9 cycles of MOPP/ABVD and extended field RT (dose of 20 Gy) and also had acute myeloid leukemia (AML) at the time of death, 25 months from diagnosis. The remaining four failures (11%) initially achieved complete remission, but relapsed at 10,

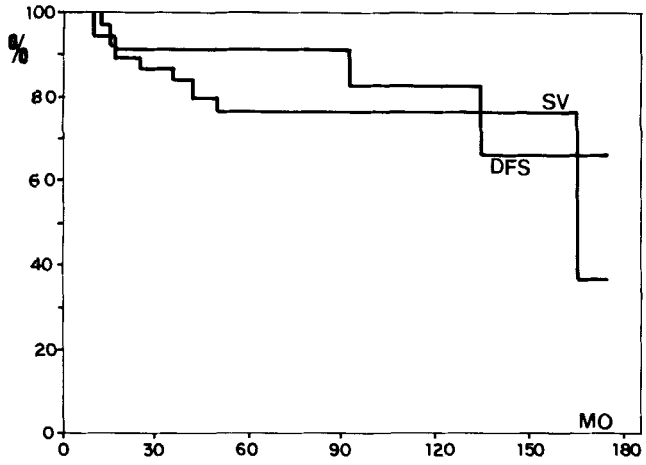

Fig. 1. Actuarial curves of overall survival (SV) (n = 37) and disease-free survival (DFS) (n = 33) of the children with Hodgkin's disease.

10, 17, and 93 months after diagnosis. They were staged as IA, IIA, IIB, and IIIB; histological subtypes were 2 NS, 1 MC, and 1 LD. These four children received salvage treatment after failure but only two were alive when the study was closed. Besides the six patients dead due to progressive disease, three more deaths occurred due to complications: two due to fatal infection (7 and 15 months from diagnosis), both with no evidence of HD; one died of AML, 49 months from diagnosis, without evidence of HD. This last child was 5 years old, NS type, stage IIB, received 3 MOPP + 2 ABVD + RT (16 Gy-extended field).

Two children, the oldest ones, treated only with extended field RT (total doses of 36 Gy to 40 Gy) had mild scapular soft tissue and bone growth alterations at 115 and 129 months of follow-up. Six children (16%) developed herpes zoster-varicella infections without late complications. Analysis of gonadal function was not done in those patients.

Histologically, initial classification was as follows: LP = 1 case, NS = 1 case, MC = 30 cases, LD = 4 cases, and 1 case unclassified (spleen). After histopathological review they were distributed as follows: no case of LP, NS = 19 (51%), MC = 14 (38%), and LD = 3 (8%). Nineteen (51%) cases changed subtype after review. MC was responsible for most of changed diagnosis: 15/30 (50%) of the cases initially diagnosed as MC were reclassified as NS after review. From these 15 cases, eight represented the cellular phase of the NS type.

DISCUSSION

As regards the relative frequency of malignant lymphomas in children, the incidence of HD is higher in underdeveloped countries than non-Hodgkin's lymphoma [1]. In some areas in Brazil, HD reaches 50% of malignant lymphomas in children [14,15] but it is difficult to obtain precise numbers because there is no national cancer registry in this country.

Mean age of CHD in underdeveloped countries is lower than in developed ones, probably because those countries have a larger infantile population [16,7]. In the present study, mean age was 7 years, similar to other Brazilian data [14,15] and lower than the mean age of 10 years found by Donaldson and Link at Stanford University, Stanford, CA, USA [18], and other underdeveloped countries [2,4].

Traditionally the male:female ratio in HD has a two- to seven-fold male predominance, either in developed or underdeveloped countries [2,4,5,8] and that was also found in our analysis: 25 boys and 12 girls, or approximately 2:1.

Survival rate of 78% at 81 months in this study was around 10–17% lower than survival rates reported in developed countries [11,18,19] but similar to survival reported in other underdeveloped countries as shown in Table II. Presence of 46% of B symptoms and 22% (8/37) of treatment failures are higher than in other series reported from developed countries [18,19]. Considering that they were appropriately managed, all this (lower survival, higher rate of B symptoms and progressive disease) may suggest a more aggressive disease in our children.

Late complications need longer follow-up for analysis. According to the Late Effects Study Group (LESG) that evaluated the risk of second malignant neoplasm in 979 children with HD diagnosed between 1955 and 1979, the estimated cumulative probability of developing any second cancer was 2% at 5 years from diagnosis, 5% at 10 years, and 9% at 15 years [20]. In 81 months of mean follow-up, we found two of 37 (5%) children with AML, 24 and 49 months from diagnosis. Both patients had advanced stage (IIIB), NS subtype, received radiation and multiple cycles of MOPP and ABVD chemotherapy, and these factors may have contributed to the development of AML [21]. Herpes zoster/varicella infections occurred in 7/37 or 20% of the children. This was similar to our previous findings in adults [22] and lower than the 36% rate mentioned by Donaldson and Link at Stanford [18].

Some explanations may be suggested to understand why CHD cases fare worse in underdeveloped countries, as observed in our report and those from other countries [2,7,8]. First, and the most obvious, is that health care in these countries is worse and patients look for medical care only when the disease is already extensive. This does not seem to be the only explanation in our series, since we had 50% of advanced stages, which is higher than the French study [19], but is similar to the findings from Stanford [18]. This group, however, presented only 18%

TABLE II. Comparison of Clinical-Pathological Data Among Different Countries in CHD

Country [reference]	Patient number	Time period	Sex (M:F)	% Stages III/IV	% of "B" symptoms	Subtypes MC/NS	% of P.D.	5-year survival (%)
Brazil [present study]	37	1978–1988	2:1	50	46	38/51	11	78
India [7]	87	1975–1982	5.5:1	46	42	46/9	20	74
Egypt [5]	242	1975–1980	3.3:1	63	51	61/14	—	—
Uganda [2]	48	1967–1977	7:1	77	65	42/21	12	67
Kuwait [8]	78	1968–1981	2:1	53	32	49/32	—	75
France [19]	157	1982–1987	—	31	32	—	3	95
United States [18]	55	1970–1983	1.8:1	50	18	20/62	4	89

of patients with B symptoms (in contrast with our 46%), only 4% of progressive disease (ours was 11%) and a 5-year survival of 89% (ours was 78%).

The second possible explanation is that underdeveloped countries have a different histological pattern of HD, i.e., a higher frequency of MC and LD subtypes [1,2]. This may not be the case for two reasons: first, after careful review of histological slides, our pattern of frequency of the different subtypes turned out to be similar to that of developed countries, i.e., predominance of NS over MC. The same was found in a study performed in Bahia, a poorer state than ours in Brazil [16]. It is even possible that the different pattern of subtypes reported in underdeveloped countries may be due to diverse histopathological diagnostic criteria [23]. This is supported by the change of HD subtype in 51% of our cases. Second, it is no longer certain that the Rye classification plays a role in providing prognostic information, as is the case with the staging of the disease [24].

The third explanation would be difficulties in administration and control of therapy, so frequent in poorer regions. This does not seem to be the case in the present series either since only patients treated and followed in our center, according to internationally accepted protocols, entered this study. As for nutritional factors that could influence response to therapy, we could not perform an objective evaluation, but none of our patients could be considered undernourished.

In conclusion, we are presently not able to explain the eventually worse evolution of our CHD cases when compared to those in the First World. Histological classification after appropriate review of the slides showed similar distribution to developing countries.

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